Background

Complex Regional Pain Syndrome (CRPS) is an umbrella term covering different clinical scenarios [1]. In its typical presentation, CRPS is a rare condition characterized by regional persisting pain, disproportionate to its underlying cause, usually coupled with sensorimotor, vasomotor, sudomotor, and trophic abnormalities. Different forms of CRPS have been identified: CRPS type I (algodystrophy); CRPS type II (causalgia); CRPS-NOS (not otherwise specified), and CRPS with remission of some features (CRSF). The pathophysiology of algodystrophy is probably related to multiple mechanisms, such as abnormal inflammation, vasomotor dysfunction, and maladaptive neuroplasticity. In most cases this condition is related to traumatic injuries or fractures, most frequently located at the distal upper limb, although in some patients no related triggering factor can be found. Algodystrophy occurrence after non-orthopedic surgery or procedures, such as percutaneous transluminal coronary angioplasty, cardiac ablation, hemodialysis, or transplantation, is rare and underestimated. Imaging can assist clinicians in the very challenging differential diagnosis of CRPS. To prevent severe and disabling consequences, international guidelines suggest a prompt multimodal approach to algodystrophy, including pharmacological (bisphosphonates, particularly neridronate) and non-pharmacological (i.e., rehabilitation interventions) measures.

Algodystrophy in the orthopedic setting

Patients experiencing CRPS type I usually report, in their medical history, a specific triggering factor, as a fracture or crash injury [7]. In particular, the most vulnerable patients seem to be those sustaining fractures of the upper extremities, especially at
the wrist [7,10]. Otherwise, when CRPS involves the lower extremities, the main risk factors are ankle or intra-articular injuries [10]. Distal injuries or fractures are more likely to provoke CRPS than proximal ones [10]. The presence of concurrent musculoskeletal disorders, such as rheumatoid arthritis, may also increase the risk [11]. Irrespective of the location, high-energy injuries, severe fractures, and prolonged general anesthesia (not regional anesthesia) are associated with a higher CRPS risk [10]. So, surgical treatment after fractures represents an additional risk factor for CRPS. Moreover, exaggerated pain in the early stage after trauma, prolonged immobilization, and pre-existing psychosocial problems can increase the risk of developing CRPS [12]. Other orthopedic conditions linked to the occurrence of CRPS are [7] carpal tunnel syndrome (7%), sharp traumas (such as incisions or amputations, 5%), and palmar or plantar fascial fibromatosis (3%).

Algodystrophy in the non-orthopedic setting

Cases of CRPS following surgery or other invasive procedures in non-orthopedic settings are rare and often underestimated [13]. Some have been described, for example, after percutaneous transluminal coronary angioplasty, coronary artery injections, cardiac ablation, fistula/graft for hemodialysis, renal and bone marrow transplantation, mastectomy, and thoracic surgery. Interestingly, in these patients CRPS often occurs in the region distal to the surgical field [13]. Veldman et al. [14] proposed some criteria for CRPS diagnosis from an orthopedic perspective, reporting, as follows, the spread of symptoms distally to the injury site: “signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury”. A possible explanation for the occurrence of CRPS after surgery lies in the skin damage, which might be the triggering event that, being able to release damage-associated molecular products, stimulates the dendritic cells and activates an adaptive immune response [15]. Moreover, release of inflammatory cytokines and activation of T-cells and B-cells lead to the production of autoantibodies and activate an inflammatory cascade [10]. The tissue damage induces an autonomic imbalance with increased sympathetic and/or reduced parasympathetic tone, causing microcirculatory alterations, and stimulating peripheral nociceptors for a prolonged time (sympatho-afferent coupling). It has been hypothesized that this pathogenic mechanism might modulate nociceptor activity through plastic structural changes, contributing to the persistence of signs and symptoms (nociclastic pain) [10]. CRPS cases have also been associated with non-surgical events [7], such as inflammation (1%), animal bites (1%), local infections (1%), and burns (0.4%). Rarely, CRPS has been attributed to vaccination/injection, spinal disc herniation, venous thrombosis in the arm, and childbirth [7]. However, in 7% of cases, no triggering event can be found (spontaneous CRPS) [7].

CRPS prediction score

Based on a large epidemiological study [7], a new tool aiming to improve diagnostic accuracy of algodystrophy (i.e., the CRPS prediction score, CPS) was proposed. It consisted of a weighted score developed considering the most and least common signs and features differentiating CRPS from other chronic pain conditions. It is worth noting that “spontaneous/uncertain causes” or “miscellaneous causes” (absence of fractures, blunt traumatic injuries, surgery, carpal tunnel syndrome, sharp traumas, palmar or plantar fascial fibromatosis, inflammation, animal bites, local infections, or burns) are strongly considered “negative predictors” for CRPS diagnosis (-4 points in CPS). This means that, according to this score, to diagnose CRPS with a non-orthopedic related cause, several typical signs/symptoms (considered as positive predictors) need to be present in order to reach the cut-off point of ≥4. Positive predictors include (in order of importance, according to their scores): increased sweating (+4 points), reduction of complex strength (handgrip/tip toe-standing; +4 points), movement initiation disorders (+4 points), increased growth of hair/nails (+3 points), livid or hyperemic skin color (+3 points), tendon reflexes decreased (+3 points), tremor (any kind, +3 points), focal (myoclonic) dystonia (+3 points), spontaneous pain sensations (+1 point), augmentation of pain (any cause, +1 point) during the night, orthostasis, nonpainful touch or cold (+1 point), edema (+1 point), swelling (+1 point), and allodynia (+1 point).

Instead, additional negative predictors are multiple location of pain (-4 points), tendon reflexes increased (-3 points), no trophic changes (-1 point), indifferent skin color (-1 point), indifferent sweating (-1 point), no temperature difference (subjective, -1 point), no sensitivity disorders at all (-1 point), no altered sensitivity during pinprick (-1 point) or during slight touch (-1 point).

The patient’s journey in algodystrophy

Patients with CRPS describe a debilitating and disappointing clinical progression, resulting in functional decline and decreased social participation [17]. Chronic pain and related symptoms affect individuality/identity, independence, and integrity, and being extensive and variable, impact all aspects of patients’ lives [17]. Patients and their partners experience isolation and depression exacerbated by dependence on others, and restrictions in work and other usual activities. Patients’ unmet needs impact their supporting partners, increasing their emotional, financial, and domestic daily burden [17].

Treatment options

Given the complexity of CRPS in many aspects, a multimodal approach is the most recommended by international guidelines, although there is considerable heterogeneity in the effectiveness of the treatments, which essentially depends on the variability in the quality of the evidence for pharmacological and non-pharmacological interventions [18]. In particular, Packman and colleagues provided practical instructions on how to operationalize the treatment and tailor it to the needs of individuals affected by algodystrophy [19]. They proposed a model for mechanism-tailored management of CPRS that may
target more effectively the individual patient’s unique needs and presentation of CRPS signs and symptoms (Fig. 1).

Indeed, since this syndrome does not involve one single mechanism, the main suggestion is that no single-treatment approach should be preferred for the management of CRPS, and that treatment approaches should not be blindly applied. Instead, each patient should be evaluated, so as to receive evidence-informed and individual-tailored interventions. In accordance with the International Classification of Functioning, Disability and Health (ICF) concept [19], CRPS treatment should be based on a comprehensive assessment of patients that considers not only signs and symptoms, but also individualized functional goals, current limitations, and barriers to therapy, and should aim not only to improve body functions and structures, but also to enhance patients’ participation and quality of life using both pharmacological and non-pharmacological approaches.

Regarding the former, an impressive number of drugs have been tested to treat CRPS. Currently, antidepressants, anti-inflammatory agents, cyclooxygenase inhibitors, bisphosphonates, gamma-aminobutyric acid analogs, ketamine, N-methyl-D-aspartate receptor antagonists, and opioids have been used to treat CRPS [17]. However, there is a general lack of scientific evidence supporting the use of many of them to reduce pain and improve functional status in CRPS. The most consistent evidence is in favor of bisphosphonates, particularly for neridronate [20]. Other invasive treatments, such as regional nerve or lumbar sympathetic blocks, have been implemented in non-responders to traditional pharmacological therapies, with poor responses in many cases [21]. As for non-pharmacological treatments, rehabilitation interventions are among those most studied, although conflicting evidence reflects the still limited knowledge about the pathogenesis and clinical presentation of CRPS [22]. Indeed, only limited high-quality or robust evidence is available to support rehabilitation interventions. Both physiotherapy and occupational therapy are frequently applied for managing CRPS, using a variety of approaches, alone or more often in a multimodal way. Physiotherapy includes manual therapy, instrumental physical therapies, massage, and therapeutic exercise [23]. One example of therapeutic exercise described for the treatment of CRPS patients is “pain exposure physical therapy” [24], a stress-loading program designed to address learned non-use by educating patients to disrupt pain-avoidance behavior (which constitutes a “false warning sign”) and resume their activities. In this approach, the workload on the affected site should be slowly increased, carefully monitoring the clinical responses, shortly after pain exposure, and the individual should return to baseline signs/symptoms, without experiencing a “flare-up”. As for mechanical stimuli, thermal (warm and cold) and vibrotactile graded stimulation should be used to address allodynia and hyperalgesia [25, 26].

Physical modalities, in particular electrotherapy (such as TENS) and pulsed electromagnetic field therapy, may help to reduce pain and improve function when combined with other interventions for CRPS type I, even though high-quality evidence is not available and a standardized treatment protocol has not yet been defined [27]. Moreover, psychological therapies, such as cognitive-behavioral therapy, operant conditioning, counseling, pain education and relaxation techniques, can be used for educating the patient, thus improving function and disability [28]. Specific rehabilitation approaches have been suggested to improve pain and function by acting on cortical processing of the affected body region; in this regard, strategies include mirror therapy, sensory motor retuning, graded motor imagery, and tactile sensory discrimination training [29]. Indeed, sequential activation of the cortical networks involved

Figure 1 Mechanism-based signs and treatments (updated from Gierthmühlen et al. and Packman et al. [5, 18])
in sensory and motor processing aims to correct sensorimotor incongruence in afferent signaling from the affected limb\(^{30,31}\). These techniques can also be applied in combination with transcranial direct current stimulation, strengthening their effects\(^{32}\).

Occupational therapy with graded patient participation in activities has also been suggested to promote progress in rehabilitation, increasing the functional demands on the affected limb\(^{33}\); this approach entails the use of activity modification, adaptive equipment, functional splitting, and retraining. Graded return to activity may improve activity limitations related to pain-related fear or kinesiophobia\(^{34}\). Kinesiophobia is a behavior manifesting an intense fear of movement and activity, which is linked to a fear of injury; it is a frequent feature of CRPS and gradually leads to learned non-use (avoidance of activities so as not to cause a flare-up of signs and symptoms) and potentially to pseudo-neglect. Graded exposure based on cognitive behavioral principles has been shown to be effective in reducing pain-related fear\(^{34}\).

CRPS treatment includes remedial or compensatory approaches, or a combination of the two, depending on the particular clinical presentation.

**Conclusions**

For physicians, algodystrophy remains a challenging condition to manage. Incomplete knowledge of its pathophysiology and unmet needs in terms of its early diagnosis result in poor effectiveness of available approaches, which aim to prevent disabling consequences. In particular, a detailed medical history should be taken, considering any potential triggering factor. Multimodal intervention, including pharmacological approaches (particularly neridronate) as well as rehabilitation techniques, remains the best treatment option to address the different impairments and functional limitations of patients affected by algodystrophy.

**References**


